21ST EDITION

Remington

The Science and Practice of Pharmacy

LIPPINCOTT WILLIAMS & WILKINS
A Wolters Kluwer Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

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Lippincott Williams & Wilkins

351 West Camden Street
Baltimore, Maryland 21201-2436 USA

227 East Washington Square
Philadelphia, PA 19106

Printed in the United States of America

Entered according to Act of Congress, in the year 1885 by Joseph P Remington, in the Office of the Librarian of Congress, at Washington DC

Library of Congress Catalog Card Information is available
ISBN 0-683-306472

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Powder Papers—Four basic types of powder papers are available.

1. Vegetable parchment, a thin, semiopaque, moisture-resistant paper.
2. White bond, an opaque paper with no moisture-resistant properties.
3. Glassine, a glazed, transparent, moisture-resistant paper.
4. Waxed, a transparent waterproof paper.

Hygroscopic and volatile drugs can be protected best by using a waxed paper, double-wrapped with a bond paper to improve the appearance of the completed powder. Parchment and glassine papers offer limited protection for these drugs.

A variety of sizes of powder papers are available. The selection of the proper size depends on the bulk of each dose and the dimensions of the powder box required to hold the number of doses prescribed.

Powder Boxes—Various types of boxes are supplied in several sizes for dispensing divided powders. The hinged-shoulder box shown in Figure 37-23F is the most popular; these have the advantage of preventing the switching of lids with the directions for use when several boxes of the same size are in the same home. The prescription label may be pasted directly on top of the lid or inside the lid. In the latter case, the name of the pharmacy is lithographed on top of the lid.

SPECIAL PROBLEMS

The incorporation of volatile substances, eutectic mixtures, liquids, and hygroscopic or deliquescent substances into powders presents problems that require special treatment.

VOLATILE SUBSTANCES

The loss of camphor, menthol, and essential oils by volatilization when incorporated into powders may be prevented or retarded by use of heat-sealed plastic bags or by double wrapping with a waxed or glassine paper inside of a bond paper.

EUTECTIC MIXTURES

Liquids result from the combination of phenol, camphor, menthol, thymol, antipyrine, phenacetin, acetanilid, aspirin, salol, and related compounds at ordinary temperatures. These so-called eutectic mixtures may be incorporated into powders by addition of an inert diluent. Magnesium carbonate or light magnesium oxide are commonly used, effective diluents for this purpose, although kaolin, starch, bentonite, and other absorbents have been recommended. Silicic acid prevents eutexia with aspirin, phenyl salicylate, and other troublesome compounds; incorporation of about 20% silicic acid (particle size, 50 μm) prevented liquefaction even under the compression pressures required to form tablets.

In handling this problem, each eutectic compound should be mixed first with a portion of the diluent and gently blended together, preferably with a spatula on a sheet of paper. Generally, an amount of diluent equal to the eutectic compounds is sufficient to prevent liquefaction for about 2 weeks. Deliberate forcing of the formation of the liquid state, by direct trituration, followed by absorption of the moist mass, also will overcome this problem. This technique requires use of more diluent than previously mentioned methods but offers the advantage of extended product stability. Thus, the technique is useful for dispensing a large number of doses that normally would not be consumed over a period of 1 or 2 weeks.

LIQUIDS

In small amounts, liquids may be incorporated into divided powders. Magnesium carbonate, starch, or lactose may be added to increase the absorbability of the powders if necessary. When the liquid is a solvent for a nonvolatile heat-stable compound, it may be evaporated gently on a water bath. Lactose may be added during the course of the evaporation to increase the rate of solvent loss by increasing the surface area. Some fluidextracts and tinctures may be treated in this manner, although the use of an equivalent amount of a powdered extract, when available, is a more desirable technique.

HYGROSCOPIC AND DELIQUESCENT SUBSTANCES

Substances that become moist because of affinity for moisture in the air may be prepared as divided powders by adding inert diluents. Double-wrapping is desirable for further protection. Extremely deliquescent compounds cannot be prepared satisfactorily as powders.

BULK POWDERS

Bulk powders may be classified as oral powders, dentifrices, douche powders, dusting powders, insufflations, and triturations.

ORAL POWDERS

Oral powders generally are supplied as *finely divided powders* or *effervescent granules*. The finely divided powders are intended to be suspended or dissolved in water or mixed with soft foods such as applesauce prior to administration. Antacids and laxative powders frequently are administered in this form.

Effervescent granules contain sodium bicarbonate and either citric acid, tartaric acid, or sodium biphosphate in addition to the active ingredients. On solution in water, carbon dioxide is released as a result of the acid–base reaction. The effervescence from the release of the carbon dioxide serves to mask the taste of salty or bitter medications.

Granulation generally is accomplished by producing a moist mass, forcing it through a coarse sieve and drying it in an oven. The moisture necessary for massing the materials is obtained readily by heating them sufficiently to drive off the water of hydration from the uneffloresced citric acid. The completed product must be dispensed in tightly closed glass containers to protect it against the humidity of the air.

Effervescent powders may be prepared also by adding small amounts of water to the dry salts to obtain a workable mass. The mass is dried and ground to yield the powder or granule. Care must be used in this procedure to ensure that the reaction that occurs in the presence of water does not proceed too far before it is stopped by the drying process. Should this happen, the effervescent properties of the product will be destroyed.

Other preparative techniques have been reported for effervescent powders such as a fluidized-bed procedure in which the powders are blended and then suspended in a stream of air in a Wurster chamber. Water is sprayed into the chamber, resulting in a slight reaction and an expansion of the particles to form granules ranging in size from 10- to 30-mesh. This approach apparently offers a number of advantages over the older techniques. The extent of reaction and particle size are controlled during the manufacture. A drying oven, trays, or even grinding devices are not required. Furthermore, the technique lends itself to a continuous as well as a batch operation.

The heat generated from the blending and mixing operation also has been used to mass the powders by causing the release of the water of hydration from the citric acid. The massed materials can be dried and sieved through a coarse sieve. This technique thus eliminates the need of an external heat source or a granulating solution.

DENTIFRICES

Dentifrices may be prepared in the form of a bulk powder, generally containing a soap or detergent, mild abrasive, and an anticariogenic agent.

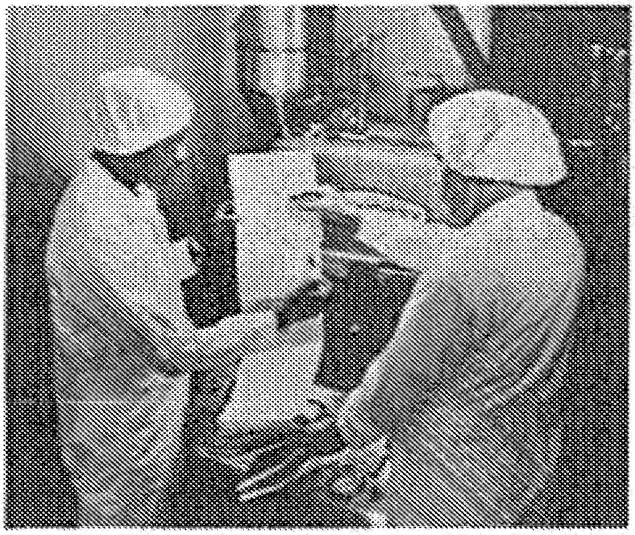

Figure 45-1. Tablet press operators checking batch record in conformance with Current Good Manufacturing Practices (courtesy, Lilly).

with the added advantage of a greatly reduced time period required for the coating operation. Advances in material science and polymer chemistry has made these coatings the first-choice of formulators.

Enteric-Coated Tablets (ECT)—These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine. Enteric coatings can be used for tablets containing drug substances that are inactivated or destroyed in the stomach, for those that irritate the mucosa, or as a means of delayed release of the medication.

Multiple Compressed Tablets (MCT)—These are compressed tablets made by more than one compression cycle. This process is best used when separation of active ingredients is needed for stability purposes, or if the mixing process is inadequate to guarantee uniform distribution of two or more active ingredients.

Layered Tablets—Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three, or more layers. Special tablet presses are required to make layered tablets such as the Versa press *(Stokes/Pennwalt)*.

Press-Coated Tablets—Such tablets, also referred to as dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets (ie, slotting, monogramming, speed of disintegration) while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is the *Manesty* Drycota. Press-coated tablets also can be used to separate incompatible drug substances; in addition, they can provide a means of giving an enteric coating to the core tablets. Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms.

Controlled-Release Tablets (CRT)—Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as *prolonged-release* or *sustained-release* dosage forms as well. These tablets (as well as capsule versions) can be categorized into three types: (1) those that respond to some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively steady, controlled manner; and (3) those that combine combinations of mechanisms to release *pulses* of drug, such as repeat-action tablets. The performance of these systems is described in more detail in Chapter 47. Other names for these types of tablets can be: *Extended Release, Sustained Release, Prolonged Release, Delayed Release*, and in the case of pulsatile tablets, *Repeat Action, Pulsatile Release* or *Pulse Release*.

Tablets for Solution (CTS)—Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed. Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tablets for Solution.

Effervescent Tablets—In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as a disintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.

Compressed Suppositories or Inserts—Occasionally, vaginal suppositories, such as Metronidazole tablets, are prepared by compression. Tablets for this use usually contain lactose as the diluent. In this case, as well as for any tablet intended for administration other than by swallowing, the label must indicate the manner in which it is to be used.

Buccal and Sublingual Tablets—These are small, flat, oval tablets. Tablets intended for buccal (the space between the lip and gum in the mouth) administration by inserting into the buccal pouch may dissolve or erode slowly; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Progesterone tablets may be administered in this way. Some newer approaches have employed materials that act as bioadhesives to increase absorption of the drug.

Some other approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride, or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly, and the drug substances are absorbed readily by this form of administration.

MOLDED TABLETS OR TABLET TRITURATES (TT)—Tablet triturates usually are made from moist material, using a triturate mold that gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water-soluble.

Dispensing Tablets (DT)—These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic Tablets (HT)—Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged, since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia.

Compressed Tablets (CT)

For medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness, and lubrication. The ingredients such as disintegrants designed to break the tablet up in gastrointestinal (GI) fluids and controlled-release polymers designed to slow drug release ideally should possess these characteristics or not interfere with the desirable performance traits of the other excipients. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material that is to be compressed into tablets.

The basic mechanical unit in all tablet-compression equipment includes a lower punch that fits into a die from the bottom and an upper punch, with a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity (Fig 45-2). The tablet is formed by pressure applied on the punches and subsequently is ejected from the die. The weight of the tablet is determined by the volume of the material that fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in ensuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper. If the tablet granulation does not possess cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the

packaging machinery requires high slip to prevent binding and is important in form–fill–seal operations.

Blocking—the tendency of two adjacent layers of film to stick together. This can create difficulties during manufacturing.

Fatigue resistance, or the ability to withstand the imposition of repetitive short-time stress or deformation without cracking, is relevant in applications involving continual cyclical loading, such as toggle mechanisms, gear teeth of a pump, or peristaltic compression of IV tubing.

Creep failure occurs when a plastic is subjected to a constant static load; it deforms quickly and elastically (reversibly) to a predicted strain value and then continues to deform at a slower rate indefinitely. Rupture may eventually occur. Creep is both temperature and time dependent. The design life of the package thus plays a role, because both strength and stiffness may be time related. The loss of torque of a static bottle-closure system over time or deformation of plastic IV tubing under constant compression are examples.

Other properties of plastics may affect their usage in a particular application. For example, low-temperature mechanical behavior is important if a plastic is exposed to freezing temperatures during its use, since the impact strength of certain plastics decreases in the frozen state. The density of plastics, which varies between 0.8 and 1.8 g/cm^3, is an important property, since lower-density materials will produce more items per unit weight. Additionally, the melting point, which may extend over a range of temperatures, is important for determining processing temperatures, heat sterilizability, ability to hot-fire a product, and heat-sealing characteristics.

Additional mechanical properties are characteristic of component subsystems or of the entire package:

Hot tack—the ability of a heat seal to remain intact as it cools down from its sealing temperature, thus preserving package integrity.

Abrasion and shock test measures the interactive effects of abrasion and shock on a form–fill–seal package.

Optical Properties

Important optical properties in plastic packaging materials are:

Light transmission—the ratio of the intensity of a light source measured with the film interposed to the intensity without the film. It gives no indication of image distortion or blurring.

Clarity—the degree of distortion of an object seen through the film.

Haze—a measure of milkiness caused by light scattering by surface imperfections or film inhomogeneities such as crystallites, voids, cross-linked materials, and undissolved additives. Haze obscures visibility for product inspection.

Gloss—measures specular reflection, or the reflectance of light as a mirror reflects. This parameter indicates the ability to produce a sharp image of any light source, giving rise to a pleasing sparkle of the film.

Electrical Properties

Electrical properties can be important, as for the dissipation of static charge in the operating room. This was previously of greater concern when ether was used more widely as an anesthetic and poured from a bottle, resulting in a potential fire hazard. More importantly, static electricity is a hazard to electronic equipment and devices. In addition, dirt and dust are attracted by static to the surface and increase the chance of contamination.

PHYSICOCHEMICAL PROPERTIES

Mass Transfer

Many pharmaceutical preparations must be protected adequately from oxygen, water vapor, carbon dioxide, and other permeants. An effervescent tablet requires a barrier to moisture, for example, whereas an oil-based product must be protected from oxygen-induced oxidation. Unlike glass, plastics are permeable. Barrier properties indicate permeability to water vapor, oxygen, carbon dioxide, etc. In addition, components of the product can permeate through the package. Examples include stabilizing agents such as parabens or antibacterials, flavorants, water vapor, and oils.

Permeation through a plastic barrier depends on the composition of the plastic, permeation area, thickness of the barrier, partial pressure differential of the permeant across the barrier, and time. Fick's law of diffusion describes these phenomena mathematically. Permeation through a plastic also can be affected greatly by additives and the crystalline structure of the plastic. Specific additives, primarily plasticizers, can increase the permeation rate greatly. Highly crystalline plastics such as polypropylene generally exhibit low water-permeation rates. An increase in the size (eg, diameter, molar volume) of a penetrant in a series of chemically similar penetrants generally leads to an increase in solubility and a decrease in diffusion coefficient. Since the permeability coefficient is related to the product of these, its variation with penetrant size is often much less.[2]

As a guide, the approximate relative permeation rates for water vapor, oxygen, and carbon dioxide through the more commonly used plastics in packaging are given in Table 54-1.[3] More extensive compilations of permeation rates for a variety of migrating molecules can be found in the *Polymer Handbook*.[4] The total ingress of gas into a package can be divided into contributions from the separate components, for example, permeation through the lid, bottle, and outer protective overpouch and gross leakage through microscopic cracks and pinholes. This analysis can be performed kinetically to verify container integrity or to resolve manufacturing problems.[5]

Chemical Attack

Resistance to acids, alkalies, fats, solvents, water, and light are important if compatibility with these materials is required. Some plastics are incompatible with plasticizers used with PVC polymers, lipid emulsions, detergents, or antiseptic solutions. Iodine-containing liquids permanently stain many polyolefin compounds after a brief exposure. Absorption of the migrating

Table 54-1. Permeability Rates of Selective Plastic Packaging Materials

	G/100 IN^2/24 HR/MIL @ 37.8°C	CC/100 IN^2/MIL/24 HR/ATM @ 25°C	
PLASTIC	WATER VAPOR	OXYGEN	CARBON DIOXIDE
Nylon			
Type 6	16–22	2.6	10–12
Type 12	4	34–92	153–336
Polyethylene terephthalate	1.0–1.3	3.0–6.0	15–25
Polyethylene			
Low density	1.0–1.5	500	2700
Medium density	0.7	250–535	1000–2500
High density	0.3	185	580
Polypropylene	0.7	150–240	500–800
Polystyrene	7–10	250–350	900
Vinyl			
Nonplasticized	2–5	4–30	4–30
Plasticized	15–40	600	20–500
Vinyl chloride-acetate copolymer			
Nonplasticized	4	15–20	40–70
Plasticized	5–8	20–150	70–800
Polyvinylidene chloride	0.2–0.6	0.8–6.9	3.8–44
Polycarbonate	11	300	1075

From *Modern Plastics Encyclopedia*, vol 64. New York: McGraw-Hill, 1987, p. 554.